Date: July 12, 2001
From: Gibbes Johnson
To: BLA #99-1470 File
Through: Amy Rosenberg, M.D., Barry Cherney, Ph.D.
Subject: Review of Sponsor's response to CR letter. The CR letter questions/issues are followed by my assessment of the sponsor's response (in bold)

ASR 11/14/01

Our STN: BL 103946/0 (replaces Ref. No. 99-1470)

Mark W. Moyer
Director, Drug Regulatory Affairs
Sanofi-Synthlabo, Incorporated
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Dear Mr. Moyer:

This letter is in regard to your biologics license application for Rasburicase submitted under section 351 of the Public Health Service Act.

The Center for Biologics Evaluation and Research (CBER) has completed the review of all submissions made relating to this application. Our review finds that the information and data submitted are inadequate for final approval action at this time based on the deficiencies outlined below.

PRODUCT AND MANUFACTURING INFORMATION

1. The assay for urate oxidase enzyme activity, used as a release test and in stability studies, is not performed under conditions which allow for a valid evaluation of the critical kinetic parameters of the test sample enzyme relative to the reference standard.

   a. Please develop an assay which is performed under the conditions of steady state kinetics, such that an initial velocity (rate) is measured and substrate concentrations do not significantly change during the course of the reaction (i.e., < 5% of substrate is converted to product). This assay should monitor the initial velocity of the reaction over a broad range of substrate concentrations. The results of this analysis

should confirm that the test sample enzyme possesses comparable values for [redacted] relative to the reference standard enzyme.

b. Please submit data from the revised assay for urate oxidase activity which support the conclusion that the enzymatic activity of drug substance production batches in the BLA are consistent and comparable to the primary and/or working reference standard.

Reviewer's assessment of response:

Urate oxidase catalyzes the conversion of uric acid and molecular oxygen to allantoin and hydrogen peroxide. A hyperuricemic patient would possess blood levels of greater than 500 uM uric acid (8 mg/0.1 liter). A [redacted] substrate concentration of [redacted] uM uric acid was utilized in the potency assay submitted to the BLA. From this assay a [redacted] is determined and must be [redacted] The drug product must contain a fixed number of units per vial. The definition of how to define [redacted] is somewhat arbitrary in that it is dependent upon the assay conditions [redacted] versa. In response to our request, the sponsor has developed an assay which measures [redacted] generation by coupling the reaction to [redacted] and detection at [redacted] nm. The one fault with this assay was the fact that only one concentration of [redacted] was used below [redacted] uM). Analysis of the reference standard and drug substance batchs demonstrated consistency with regard to [redacted] Using this data the sponsor demonstrates that [redacted] yields the same [redacted] determined with the "old" assay. This would be expected and a major problem if not true.

However, the sponsor proposes to retain the old assay as a release specification assay and in ongoing stability studies. They propose, however, to evaluate the activity of [redacted] batchs of urate oxidase, at [redacted] high concentration of uric acid using the old and new assay with post-approval review. This might be of value since in vivo levels of uric acid are relatively high.

In addition, the following should be considered:

a. From a drug substance manufacturing perspective a thorough evaluation of enzymatic parameters such as [redacted] is of value to confirm consistency.

b. The complexity of the enzyme assay should be considered. In this instance, it is a simple assay and evaluation of activities as a function of [redacted] is straightforward and thus, not unreasonable.

[redacted]

d. Since blood uric acid levels in patients are well above the [redacted] perhaps we need to only be concerned about enzyme activity at high concentrations of uric acid, i.e. a potency assay at a [redacted] high concentration of uric acid.

[redacted]

The sponsor's response and proposals are unacceptable. The sponsor should comply with our request in the CR letter and replace the old assay as a release specification and in all future stability studies. However, based upon the information provided in their response, a post-approval commitment would be acceptable.

2. The process validation described in the BLA for defining the lifetime of the purification columns and membranes used in commercial production of drug substance is based solely on the results of a limited number of in-process tests. The majority of these in-process tests reveal little information regarding performance of the purification step and/or purity of Rasburicase. Please develop a more rigorous validation plan which monitors column/membrane performance and impurity profiles to define the lifetimes of purification columns and membranes used in the production of drug substance.

Reviewer's assessment of response:

The sponsor presented a clear validation plan for determination of the column/membrane lifespans at commercial scale. The in-process testing

which is performed for each step of purification and used in this determination is summarized as follows:

The sponsor has generated a significant amount of commercial scale experience and trend analysis for each step was presented and supported [redacted] cycles for each step. The maximum number of lifespans has yet to be established, but the prospective plan presented is acceptable.

3. Please demonstrate the cleaning effectiveness of skids, chromatography columns and [redacted] membranes used in the purification of drug substance at the commercial scale. We suggest you conduct periodic mock/sham purifications (buffers only) over the intended life span of the column and membranes. Please be sure to inject sample/equilibration buffer into the system in an identical manner to that performed in the purification of drug substance at the commercial scale (identical vessels and introduction of sample to controllers and pumps). In the event that any material is detected, the identity of this

material should be determined and the impact of this potential contaminant on the product purified after the last mock/sham run should be investigated.

Reviewer's assessment of response:

The sponsor has developed a plan to address our concerns. In summary, a blank run will be performed every [redacted] cycles and analysis [redacted] will be performed. In addition, [redacted] will be monitored. The detection of any contaminant will initiate the appropriate investigation. This response is acceptable.

4. Release testing focuses primarily on an analysis of drug substance [redacted] with little attention given to addressing [redacted] To address these concerns:

   a. Please include an evaluation of the complete [redacted] as part of the acceptance criteria for release tests.

   b. In the [redacted] analysis used as a release and in-process test, please include an additional [redacted] to confirm the absence of potential impurities [redacted]

   c. Similarly, in the [redacted] please include an additional gradient [redacted]

Reviewer's assessment of response: The sponsor has modified the acceptance criteria for the [redacted] release assays, but not for [redacted] release test. However, the translated SOP states [redacted]". This a complicated issue because often [redacted] which are unrelated to drug substance [redacted] On the other hand, a contaminant which [redacted] cannot be simply dismissed without some additional information. The sponsor should set a limit on [redacted] which are significantly different between blank/reference standard runs and test sample runs.

With regard to items b and c (above) the sponsor modified the [redacted] and analyzed the [redacted] drug substance batchs and reference standard, and did not detect any additional contaminants. For this reason,

the sponsor sees no value in these modified analyses. Unfortunately, the sponsor missed the main point of our request. In other words, if contaminants existed, could they be detected with the purity analyses in place? It would depend upon the contaminant. However, purity assays should cast as broad a net as possible to detect contaminants and we are just requesting a modification of the current assay. This response is not acceptable. A post-approval commitment would be acceptable.

5. It is not known whether Rasburicase acetylation has any effect on enzymatic activity. Due to this fact, please monitor for the presence of the non-acetylated amino terminal peptide (non-acetylated [redacted] in the [redacted] and set specifications as a part of drug substance release testing to confirm complete acetylation of Rasburicase.

Reviewer's assessment of response: Further analysis demonstrated that a typical batch of rasburicase contains [redacted]% acetylated [redacted] The sponsor demonstrated the ability to monitor the non-acetylated [redacted] in the [redacted] analysis. Accordingly, the release control monograph was modified to monitor the presence of the non-acetylated peptide. This response is acceptable.

6. For the designation of a working reference standard (relative to primary reference standard), please include a co-mixture evaluation of primary reference standard and test sample in a [redacted]

Reviewer's assessment of response: The sponsor has modified the method for the designation of a working reference standard. This response is acceptable.

7. In all [redacted] release tests for the drug product, please include a control analysis of [redacted] alone. The acceptance criteria should include a consideration of potential impurities and related substances which [redacted]

Reviewer's assessment of response: The sponsor believes that since a blank, reference standard and test sample are run and compared, an additional analysis of [redacted] alone is redundant. There is validity to this argument. However, as in item #4 above, the SOP for acceptance states to [redacted] and should be addressed as described in item #4 above. With exception of this last point, the response is acceptable and the last point could be addressed as a post-approval commitment.

8. Please submit updated stability data for drug substance batches [redacted] to support the requested 12 month expiration dating period.

Reviewer's assessment of response: The results demonstrated that storage at [redacted]C for [redacted] months is acceptable and supports the [redacted] month expiration. In contrast, storage at [redacted]C is not supported. This response is acceptable.

9. We note that [redacted] produced in 1989 was used in the generation of the master cell bank (MCB). The material was derived from non-neural bovine tissue, partially of French origin. Although BSE was not identified in France until 1991 and the material was certified to be from healthy herds which were free of BSE as of January 2, 1993, there is a remote possibility that the [redacted] used to generate the MCB is contaminated with the agent responsible for BSE. To assist in our assessment of the potential health hazard associated with possible contamination, please address the following:

   a. What evidence exists to support the argument that the agent responsible for BSE cannot propagate in yeast?

   b. Does the process used for manufacture of [redacted] from bovine tissues inactivate the agent responsible for BSE?

   b. What specific bovine tissues were used in the generation of the [redacted]

Reviewer's assessment of response: Propagation of the agent requires the biosynthesis of the Prp protein in mammalian cells. Since yeast do not express the Prp protein or any related protein (complete genome is known) propagation would not appear to be possible. In addition, uptake of proteins in yeast is limited to very small peptides and thus, cytosol to cytosol transfer also is very unlikely. [redacted] is derived from a [redacted] is generated via relatively harsh treatment of [redacted] A reference is cited which suggests this treatment inactivates the BSE agent. [redacted] is contained in the [redacted] and has been shown to inactivate the agent responsible for scrapies. [redacted] were used as a source of [redacted] and EU classified as class 4 (no detectable infectivity). I would note that I believe that [redacted] is a source of the agent. Nevertheless, based upon this information and the highly purified nature of rasburicase, the potential risk of contamination from the MCB (note: bacto peptone is not in WCBs) is extraordinarily low. This response is acceptable.